

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

| | | | |
|--|--|--|------------------|
| Applicant's or agent's file reference 4313-4610PC | FOR FURTHER ACTION | | See item 3 below |
| International application No. PCT/IB2006/002028 | International filing date (<i>day/month/year</i>) 25 July 2006 (26.07.2006) | Priority date (<i>day/month/year</i>) 26 July 2005 (26.07.2005) | |
| International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237 | | | |
| Applicant BIOREST LTD. | | | |

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- | | |
|---|---|
| <input checked="" type="checkbox"/> Box No. I | Basis of the report |
| <input type="checkbox"/> Box No. II | Priority |
| <input checked="" type="checkbox"/> Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement |
| <input type="checkbox"/> Box No. VI | Certain documents cited |
| <input type="checkbox"/> Box No. VII | Certain defects in the international application |
| <input type="checkbox"/> Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis.2).

Date of issuance of this report
27 November 2006 (27.11.2006)

Authorized officer

Cecile Chatel

The International Bureau of WIPO
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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITYTo:
DOROTHY R. AUB
MORGAN & FINNEGAN, LLP
3 WORLD FINANCIAL CENTER
NEW YORK, NY 10281-2101

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year) 29 JUL 2008

FOR FURTHER ACTION

See paragraph 2 below

Applicant's or agent's file reference

4313-4019PC

International application No.

PCT/IB06/02028

International filing date (day/month/year)

25 July 2006 (25.07.2006)

Priority date (day/month/year)

26 July 2005 (26.07.2005)

International Patent Classification (IPC) or both national classification and IPC

IPC: A61N 43/00 (2006.01); A61K 31/33 (2006.01)

USPC: 514/183

Applicant

BIOREST LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(c)(1) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(2) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioners for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Date of completion of this
opinion

12 June 2008 (12.06.2008)

Authorized officer
Adam Marschke

Telephone No. (571) 272-1600

Postfile No. (571) 273-2201
Form PCT/ISA/237 (cover sheet) (April 2007)

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/IB06/02028

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

- 2.
- ☐
- This opinion has been established taking into account the rectification of an obvious mistake authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a)).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established on the basis of:

a. type of material

- ☐ a sequence listing
☐ table(s) related to the sequence listing

b. format of material

- ☐ on paper
☐ in electronic form

c. time of filing/furnishing

- ☐ contained in the international application as filed.
☐ filed together with the international application in electronic form.
☐ furnished subsequently to this Authority for the purposes of search.

- 4.
- ☐
- In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/IB2006/2028

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 32-37

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international search (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 32-37 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 32-37 are improper multiple dependent claims, and thus were not examined with respect to novelty, inventive step, or industrial applicability.

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2006/020228

| | | |
|--|---|--|
| Box No. V Reasoned statement under Rule 43 bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement | | |
| 1. Statement | | |
| Novelty (N) | Claims Please See Continuation Sheet _____ YES Claims Please See Continuation Sheet _____ NO | |
| Inventive step (IS) | Claims Please See Continuation Sheet _____ YES Claims Please See Continuation Sheet _____ NO | |
| Industrial applicability (IA) | Claims Please See Continuation Sheet _____ YES Claims Please See Continuation Sheet _____ NO | |
| 2. Citations and explanations: | | |
| <p>Claims 1, 4-8, 10-16, 20, 24, 27-29, 38, and 41 lack novelty under PCT Article 33(2) as being anticipated by Shi et al. (US 6,770,466). Shi et al. teaches encapsulating the active ingredients into a liposome (col 83) and teaches aspirin (col 174) as well as mitomycin and 5-fluorouracil (col 51-52) and paclitaxel (col 119). Shi et al. teaches particle sizes of 0.2 microns and lower (col 173) and they teach the usefulness of their invention for treatment of ischemic-reperfusion injury (col 91-92).</p> <p>Claims 2-3, 9, 17-19, 21-23, 25-26, 30-31, 39-40, 42-43 lack an inventive step under PCT Article 33(3) as being obvious over Shi et al. (US 6,770,466) in view of Danenberg et al. (US 2004/0265391 A1). Shi et al. teaches encapsulated active ingredients in liposomes, however they do not teach embedded or particulated ingredients. Danenberg et al. teaches encapsulated bisphosphates, embedded bisphosphates, and particulate bisphosphates (page 3 [0028]). They further teach that these bisphosphates can be used to treat myocardial infarction (claim 29) including reducing the zone of infarct (claim 68). They also teach plateletoma, one of the bisphosphates claimed by applicant in claim 19 (page 4, [0035]). Danenberg et al. further teaches liposomes, microparticles, nanoparticles, and aggregates (page 3, [0025]). Since both methods are treating myocardial infarction and ischemic-reperfusion injury, and both have active ingredients encapsulated in liposomes, it would be obvious for one of ordinary skill in the art at the time of the invention to also use the formulations of Danenberg et al. in the method of Shi et al.</p> <p>Claims 1-31, 38-43 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry for treatment of heart related disorders and as a drug delivery system.</p> | | |

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITYInternational Application No.
PCT/IB06/02028

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

V.I. Reasoned Statements:

The opinion as to Novelty was positive (Yes) with respect to claims 2-3, 9, 17-19, 21-22, 25-26, 30-31, 39-40, 42-43

The opinion as to Novelty was negative (No) with respect to claims 1, 4-8, 10-16, 20, 23-24, 27-29, 38, 41

The opinion as to Inventive Step was positive (Yes) with respect to claims NONE

The opinion as to Inventive Step was negative (NO) with respect to claims 1-31, 38-43

The opinion as to Industrial Applicability was positive (YES) with respect to claims 1-31, 38-43

The opinion as to Industrial Applicability was negative (NO) with respect to claims NONE

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | | |
|--|---|--|--|
| Applicant's or agent's file reference 4313-4010PC | FOR FURTHER ACTION | | see Form PCT/ISA/220 as well as, where applicable, Item 3 below |
| International application No. PCT/IB06/02028 | International filing date (day/month/year) 25 July 2006 (25.07.2006) | (Earliest) Priority Date (day/month/year) 26 July 2005 (26.07.2005) | |
| Applicant BFOREST LTD | | | |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the Report

- a. With regard to the language, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.
☐ a translation of the international application into _____, which is the language _____

of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

- b. ☐ This international search report has been established taking into account the **rectification** of an obvious mistake authorized by or notified to this Authority under Rule 91 Rule 43.6 bis(a)

- c. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☒ Certain claims were found unsearchable (See Box No. II)

3. ☐ Unity of invention is lacking (See Box No. III)

4. With regard to the title,

☒ the text is approved as submitted by the applicant.
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____
☐ as suggested by the applicant.
☐ as selected by this Authority, because the applicant failed to suggest a figure.
☐ as selected by this Authority, because this figure better characterizes the invention.
- b. ☒ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB06/02028

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 31-37
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

- Remark on Protest** ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB06/02025

A. CLASSIFICATION OF SUBJECT MATTER

IPC: A61N 43/00(2006.01); A61K 31/03(2006.01)

USPC: 514/183

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S.: 514/183

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|--|
| x | US 6,770,466 B2 (Shi et al.) 3 August 2004 (03.08.04), col. 51, line 64 thru col. 52 line 20, col. 83, lines 10 thru col. 83 line 20; columns 91-92; col. 100, col. 119 lines 30-45; | 1, 4-16, 20, 23-24, 27-29, 31, 38, 41 |
| y | col. 173 lines 5-11; col. 174 lines 10-45; | 2-3, 17-19, 21-22, 25-26, 30, 39-40, 42-43 |
| y | US 2004/0265391 A1 (Danenberg et al.) 30 December 2004 (30.12.04), page 3 [0028], and claims 29, 68. | 2-3, 17-19, 21-22, 24-30, 39-40, 42-43 |

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

Special categories of cited documents.

"A" document defining the general state of the art which is not considered to be of particular relevance

"P" prior documents published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"E" earlier application or patent published on or after the international filing date

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is considered with one or more other such documents, such combinations being obvious to a person skilled in the art

"O" document referring to an oral disclosure, use, exhibition or other means

"A" document member of the same patent family

"P" document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search

Date of mailing of the international search report

12 June 2008 (12.06.2008)

29 JUL 2008

Name and mailing address of the ISA/US

Authorized Officer

Mail Stop PCT, Attn: ISA/US

Ardin Marschel

Commissioner for Patents

P.O. Box 1430

Alexandria, Virginia 22313-1430

Facsimile No. (571) 273-3701

Telephone No. (571) 272-1600

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB06/02028

Continuation of B. FIELDS SEARCHED Item 3:

EAST, CAPLUS, MEDLINE, DRUG, EMBASE, BIOSIS

Search Terms: embedded bisphosphate, encapsulated bisphosphate, particulate bisphosphate, ischem-reperfusion injury, aspirin, clodronate, microparticles, aggregates, liposome